Selenium and the thyroid

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Purpose of review
This article provides an update on the role of the essential trace element selenium and its interaction with the other trace elements iodine and iron that together contribute to adequate thyroid hormone status. Synthesis, secretion, metabolism and action of thyroid hormone in target tissues depend on a balanced nutritional availability or supplementation of these elements. Selenium status is altered in benign and malignant thyroid diseases and various selenium compounds have been used to prevent or treat widespread diseases such as goiter, autoimmune thyroid disease or thyroid cancer.

Recent findings
Several studies, most with still too low numbers of cases, indicate that selenium administration in both autoimmune thyroiditis (Hashimoto thyroiditis) and mild Graves' disease improves clinical scores and well-being of patients and reduces thyroperoxidase antibody titers. However, published results are still conflicting depending on basal selenium status, dose, time and form of selenium used for intervention. Evidence for sex-specific selenium action, lack of beneficial effects in pregnancy and contribution of genetic polymorphisms (selenoprotein S) has been presented.

Summary
Adequate nutritional supply of selenium that saturates expression of circulating selenoprotein P, together with optimal iodine and iron intake, is required for a healthy and functional thyroid during development, adolescence, adulthood and aging.

Keywords
autoimmune disease, goiter, selenoprotein, thyroid cancer, thyroiditis, trace element

INTRODUCTION

Iodine deficiency disorders are still prevailing in many regions of the world including developed countries with affluent health systems [1▪▪,2–4]. Although WHO and the Iodine Global Network have been very successful in increasing public and political awareness of the deleterious impact of inadequate iodine intake for fetal and postnatal brain development and intelligence quotient, iodine deficiency disorders have not been eradicated yet. Evidence suggests that even with adequate iodine intake, thyroid development and function might be impaired by concomitant deficiencies of several other essential trace elements required for synthesis, secretion, metabolism and action of thyroid hormone. Apart from iodine, selenium, iron, zinc, copper and calcium are involved in control of this hormone network, and especially selenium and iron are limiting nutritional factors as shown by epidemiology and intervention studies in benign thyroid diseases [5–13,14▪,15,16]. Thyroid diseases have high prevalence and represent a significant cost factor and burden for health and economic systems as they require regular diagnostic tests, therapy or medical monitoring and intervention [18–21]. As L-thyroxine still ranks among the top 10 drugs prescribed by physicians in many countries mainly for patients with autoimmune thyroiditis and after thyroidectomy [17,20,21], a higher awareness of crucial interactions between nutritional, environmental and genetic components affecting and regulating thyroid hormone function is mandatory and systematic screening of thyroid function in pregnant women is discussed [22▪]. Both excess and deficiencies of these trace elements impair thyroid function and significant additive or antagonistic interactions have been described, indicating the need in obtaining an adequate balance achieved by either nutritional intake or additional

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KEY POINTS

- Adequate selenium supply ensures a normal thyroid hormone status and preserves integrity of the thyroid gland exposed to H_2O_2, excess stimulation by thyrotropin (TSH) or TSH receptor-stimulating antibodies (TRAK), or attack by the immune system in autoimmune thyroiditis.
- Epidemiological and interventional studies support a key role of selenium as well as iodine and iron trace element status for thyroid function.
- Selenium supplementation in autoimmune thyroiditis and mild Graves' disease appears to defer loss of thyroid function.
- Molecular and cellular mechanisms of beneficial selenium effects depend on the intact thyroid angiofollicular units, the thyroid-targeting immune system as well as endogenous (sex steroid hormones) and exogenous factors (endocrine disrupters).
- As for other endpoints, the dose–effect, benefit–risk relationship of selenium status for thyroid function exhibits a typical J-type curve, with an optimal serum selenium concentration at 125 μg selenium per liter.

supplementation. Adequate or elevated supply of one trace element (e.g. iodine) might unmask underlying deficiencies in the nutritional supply of others (e.g. selenium or iron), thus leading to impaired thyroid function or even tissue damage [7–13,14▪,15,16]. On the contrary, altered macronutrient intake and changing eating habits accompanying economic development in many rural societies might require additional trace element supplementation to ensure increased thyroid hormone production associated with higher food and calorie intake. Studies in developing countries have shown that iron, essential for efficient iodine utilization and thyroid hormone synthesis, might be nutritionally deficient in many parts of the world and thus impair thyroid hormone synthesis, storage and secretion even if iodine supply is adequate [12,13,14▪]. Similar interactions are known between selenium and iodine, as excess selenium intake is known to aggravate consequences of iodine deficiency in endemic regions, whereas adequate selenium supply attenuates adverse effects of iodine excess on the thyroid gland, preventing inflammation, fibrosis and destruction in animal models [5–10,23–25]. Such observations in sophisticated experimental animal models as well as interventional studies in regions of endemic imbalance of trace element supply or genetically susceptible risk groups or populations provide strong evidence for the need to carefully consider, monitor and – if necessary – intervene in these relevant interactions between nutritive, environmental and hormonal factors in maintenance and regulation of thyroid function and thyroid hormone action on development, growth, metabolism and homeostasis.

Pharmacological or nutritional exposure to iodine excess has been connected with manifestation of some thyroid diseases or altered disease patterns such as transiently increased incidence of autoimmune thyroid disease [26▪▪,27], autonomous thyroid nodules and papillary thyroid carcinoma [28], whereas the incidence of the more problematic variant of follicular thyroid cancer is decreasing similar to goiter incidence and volume and impaired brain development. The molecular basis of decreased ratio of follicular/papillary thyroid cancer with unaltered total incidence is not clear. Enhanced iodine supply, possibly in context with inadequate intake of the other protecting trace elements selenium and iron, may unmask autonomy of thyroid nodules and various pre-existing thyroid diseases, which then manifest as structural changes, somatic mutations and dysfunction of thyroidal tissue stressed under the preceding pressure of long-standing iodine deficiency, elevated thyroid-stimulating hormone (TSH) and enhanced H_2O_2 formation. Generally, the benefits of adequate iodine intake by far outweigh side-effects of iodine excess, which may cause problems if administered at those high gram doses contained in various medical products and drugs (iodinated X-ray contrast agents, amiodarone etc.) [29]. Monitoring of iodine deficiency is still required and includes determination of increased thyroid volume by ultrasound, decreased urinary iodine excretion normalized to creatinine clearance, or analysis of serum thyroglobulin concentration, which is increased in iodine deficiency [30].

SELENIUM AND SELENOPROTEINS AS RELEVANT CONSTITUENTS OF FUNCTIONAL THYROID TISSUE

The thyroid gland in humans and several species is unique as the tissue with the highest selenium content per tissue unit [7] retaining selenium and expressing selenoproteins even under conditions of severe deficiency similar to testis, brain and several other endocrine organs [7,31,32▪,33▪▪,34]. Although some other tissues also accumulate significant selenium concentrations with increasing age because of deposition of insoluble cadmium, mercury and lead selenides (e.g. kidney and pituitary) [7,35], the majority of thyroid selenium is contained in functional selenoproteins of thyrocytes [31,36–38]. These observations revealed another level of complexity in the tissue-specific supply of selenium compounds

under conditions of inadequate intake, the so-called tissue hierarchy of selenium supply.

The cellular uptake of various selenium compounds is not fully understood. Although selenite and selenate are transported via sulfate/sulfite sodium-dependent transport systems, the uptake of mixed selenosulfides, such as selenium-glutathione conjugates, is unclear [38,39]. One major cellular uptake mechanism for selenium involves selenoprotein P, a selenoprotein secreted by the liver and circulating in blood, wherein it constitutes up to 70% of selenium content. Selenoprotein P contains up to 10 selenocysteine residues in humans and acts as selenium delivery and storage protein [40–42]. Apolipoprotein E2 (ApoE2) receptor and/or megalin receptor-mediated selenoprotein P uptake has been described for several tissues such as testis and kidney but not for thyrocytes [33▪▪,41–45]. Surprisingly, knockout of selenoprotein P, which impairs selenium status of several tissues such as kidney, testis and others [41], does not affect selenium content and selenoprotein function in the thyroid gland. Thyroidal selenium uptake appears to be independent of selenoprotein P-mediated selenium supply, and thus resembles to some extent the brain, which is independent of hepatic selenoprotein P supply, and influenced more by a local independent and/or backup selenoprotein P synthesis and transport system [46,47]. Maternal–fetal selenium transfer across placenta also involves the selenoprotein P–ApoE2 receptor pathway [48].

Expression of most known selenoproteins has been demonstrated in the thyroid gland of several species at the transcript, the protein or functional levels [31,36–38]. Surprisingly then, genetic inactivation of selenoprotein biosynthesis by inactivation of tRNA[(Ser)]Sec selectively in thyrocytes revealed only a very minor phenotype with respect to thyroid cell biology and function [31]. This genetic inactivation led to the lack of expression of all selenoproteins, such as glutathione peroxidases (GPxs), thioredoxin reductases and deiodinases in thyrocytes. However, absence of these selenoproteins did not impair the organization of the thyroid gland, its essential angiofollicular unit, or colloid deposition. Although expression of selenoproteins could not be demonstrated in thyrocytes, no major morphological changes associated with documented enhanced reactive oxygen species (ROS), oxidative stress, structural damage, nor significant invasion of immune cells were observed. Even a strong goitrogenic challenge in these animals on low iodine intake by administration of perchlorate and antithyroid drugs did not lead to the expected worsening of the phenotype; only minor structural changes, slightly elevated TSH and normal serum thyroid hormone levels were observed in older animals [31].

This outcome of gene inactivation in transgenic mice was unexpected and is inconsistent with several studies that had demonstrated protective and preventive effects of adequate selenium supply on thyroid function in animal models and humans, in which adequate selenium intake has been demonstrated to improve structural and functional integrity of the angiofollicular functional unit and the structure of the thyroid gland [5–7,25,38]. Therefore, several questions remain to be addressed in future studies. Do (mouse) thyrocytes express a further backup system independent from the first-line antioxidative defense system provided by GPx and thioredoxin reductase selenoproteins to cope with iodine deficiency, TSH or TRAK stimulation or oxidative stress? Are beneficial effects of selenium compounds observed in goiter prevention, improvement in autoimmune thyroid disease or prevention of thyroid cancer in humans and experimental animal models mediated by endothelial cells or cells of the immune system? Are there species differences in expression, function and regulation of selenoproteins in thyrocytes?

SELENIUM BIOLOGY AND SELENOPROTEIN BIOSYNTHESIS

The biological impact of a rare genetic defect in selenoprotein biosynthesis presents as altered thyroid hormone status and developmental impairments related to deficient thyroid hormone synthesis and action [38,49▪,50–53] accompanied by further clinical signs of tissue-specific impairment of selected selenoproteins [50–53]. Thus, it was a surprising discovery that compromised function of selenocysteine insertion sequence-binding protein 2 (SBP2), essential for cotranslational incorporation of selenocysteine into selenoproteins, was initially identified by elevated T4 and TSH but low T3 levels [49▪,50–53]. In these rare cases, increased selenium intake only partially rescued the impaired synthesis of selenoproteins, as documented in a Saudi Arabian family [54]. Depending on the severity of impaired SBP2 function, the phenotype appears to be variable, and transgenic mouse models supported the interpretation of SBP2 as a limiting factor in the biosynthesis of several selenoproteins and impaired thyroid hormone activation and function [38,55,56].

Apart from their thyroid hormone-related phenotype, these patients may present with sensorineural hearing loss, impaired bone development and maturation, aspects of myopathy also found in patients with mutations in the selenoprotein N gene

(*SEPN*) [57], various signs of impaired brain development and motor function, ultraviolet-sensitive skin, altered immune function and a remarkable redistribution of white body adipose tissue from the visceral compartment to subcutaneous fat, resulting in high insulin sensitivity [49▪,50–53]. Several of these clinical aspects are probably not directly related to altered thyroid function but to impaired tissue-specific expression of other selenoproteins. In one case, growth retardation was responsive to growth hormone (GH) treatment, which also decreased serum TSH but did not normalize serum free T4 and free T3 concentrations [53], suggesting persistently impaired hepatic deiodinase 1 activity, which typically responds to GH in adolescent and adult GH-deficient patients with normal selenium homeostasis [58–60].

Cell culture experiments and experimental transgenic animal models in which selenium status can be manipulated to an extent incompatible with long-term survival of the mice or humans have revealed important insight into tissue-specific expression and function of selenoproteins, including the three deiodinase enzymes [7,31,45,56]. Remarkably, a pronounced tissue-specific, development-associated and disease-dependent deiodinase expression pattern has been described. These experiments have indicated that among several selenoproteins expressed in tissues and cells, deiodinases rank rather high in availability of limiting amounts of selenium required for their biosynthesis and function [7,38]. In several tissues, more abundant selenoproteins such as GPx1 and other selenoproteins might even provide sufficient selenium locally liberated during their proteosomal or lysosomal turnover, thus enabling cellular deiodinases and other highly essential selenoproteins such as thioredoxin reductases and GPx4 to be synthesized and remain functional, whereas other selenoproteins' expression is decreased or severely impaired [7,38,33▪▪,61].

THYROID HORMONE DEIODINASES ARE SELENOPROTEINS

All three deiodinases, the key enzymes catalyzing thyroid hormone activation to the thyromimetically active T3 as well as inactivation of T3 and its prohormone T4, were identified as selenocysteine-containing proteins [7,62–64]. Also GPxs, highly expressed in the thyroid gland, are selenoproteins involved in degradation of H_2O_2 and lipid peroxides together with the thioredoxin reductase selenoprotein family [7,38].

Deiodinases and the other selenoproteins encoded by 25 genes in humans contain essential selenocysteine residues in their active site. Thus, initial cell culture and animal experimental studies indicated that adequate nutritional selenium supply appears to limit expression of functional deiodinases during development and in the adult organism [7,47,65–67]. However, the deiodinative turnover of thyroid hormones requires only minimal amounts of active enzymes, in contrast to enzymatic pathways acting on abundant metabolic intermediates (e.g. carbohydrate, fatty acid, amino acid or proteins). This might be one of the reasons why inadequate intake of the essential trace element selenium does not initially manifest as impaired deiodinase activity, but rather affects those metabolic pathways, which are catalyzed by more abundant selenoenzymes acting at higher substrate concentrations. These include GPxs and thioredoxin reductases involved in cellular redox control, several endoplasmatic reticulum-associated selenoproteins as well as selenoprotein N, all of which contribute to protein biosynthesis or represent structural components of cells and tissues [68▪,69,70,71▪].

SELENIUM AND MYXEDEMATOUS CRETINISM

The role of an adequate selenium supply in achieving normal thyroid function had been discovered during the 1980s by investigators in Brussels, who identified selenium deficiency as a key factor in the development of myxedematous cretinism in Central Africa [7,23]. Combined selenium and iodine deficiency, further deteriorated by food containing goitrogens, provoke myxedematous cretinism. Animal experimental data supported this hypothesis based on human pathophysiology, demonstrating more pronounced thyroid and developmental damage in animals deficient in iodine and selenium [23,72]. Transforming growth factor β-dependent processes contribute to thyroid tissue damage initiated by high TSH levels with subsequently enhanced production of H_2O_2, ROS and reactive oxygen intermediates [8]. Adequate selenium status prevented these damaging effects even if high iodine doses were administered in rodent models of thyroid involution after long-standing iodine deficiency [7–9,23,24,72]. In contrast, results from iodination programs in Zaire have suggested that selenium supplementation under conditions of inadequate iodine intake might initially worsen thyroid dysfunction, and thus it has been recommended that adequate iodine status has to be established prior to increasing selenium intake [23]. A possible mechanism of such adverse selenium effects has been proposed. Selenium-induced activation of

peripheral thyroid hormone metabolism by deiodinase selenoproteins may lead to higher thyroid hormone turnover, deiodination and renal loss of iodide [7]. Enhanced thyroid hormone turnover and iodide loss have only been reported in individuals with very severe deficiencies of both trace elements but not among those with mild selenium and iodine deficiency or intake at the lower recommended reference levels.

DOES ADEQUATE SELENIUM INTAKE AND EXPRESSION OF SELENOPROTEINS IN THYROCYTES PROTECT FROM TYHROID DISEASE?

Adequate selenium intake increases the efficiency of thyroid hormone synthesis in animal studies [73]. The hemoprotein thyroperoxidase (TPO), which requires sufficient intake of the trace element iron, catalyzes iodide oxidation, organification and coupling of iodinated tyrosyl residues to generate iodothyronines that are still part of the thyroid hormone synthesis and storage protein thyroglobulin. One hypothesis might be that excess H_2O_2, known to inactivate TPO, might be degraded by the selenoprotein GPx3, which is secreted into the colloid lumen by thyrocytes [36]. Furthermore, TSH-stimulated excess H_2O_2 and ROS such as OH-radicals, O_2-radicals and others, not fully consumed during thyroid hormone synthesis in iodine deficiency, might be degraded by the antioxidative enzymatic defense line mounted by cellular GPxs, thioredoxin reductases, superoxide dismutases and catalase, all of which are expressed in thyrocytes [31,37]. Adequate selenium intake and supply in the thyrocytes might improve function of selenium-dependent quality control proteins (selenoprotein p15 and selenoprotein S) located at the endoplasmic reticulum [38,74,75]. They might improve synthesis, post-translational modification and apical secretion of the large dimeric glycoprotein thyroglobulin into the colloid lumen. Adequate GPx and thioredoxin reductase functions might also prevent cellular damage exerted by radical or redox cycling reactions, depending on Fe^{2+}–Fe^{3+} ions liberated from hemoprotein TPO [12,13], especially under conditions in which TPO is inactivated by excess H_2O_2.

Recently, several selenium-based analogs of antithyroid drugs have been developed and tested with respect to their inhibitory potencies on TPO and deiodinases or as synthetic mimics of these selenoproteins [76,77▪,78,79]. Structure–activity relationships were identified, providing relevant information on the mechanism of action of TPO and deiodinases, as well as allowing development and testing of selenium-based antithyroid drugs that selectively interfere with TPO or deiodinases [76,77▪,79]. As the currently used antithyroid drugs, which are based on thiourea pharmacophores (e.g. methimazole or thiouracil derivatives), exhibit significant and frequent side-effects [80], the design, development and validation of novel antithyroid compounds blocking either thyroid hormone biosynthesis and/or thyroid hormone activation is of high medical interest. Hyperthyroid diseases due to autonomous thyroid function, Graves' disease and/or drug-induced and iodine-induced hyperthyroidism may be potential targets [81].

SELENIUM STATUS, THYROID FUNCTION AND THYROID DISEASE

The first large interventional study using a combination of trace elements and vitamins, Supplémentation en Vitamines et Minéraux Antioxydants (SUVIMAX), revealed that inadequate selenium intake is associated with increased thyroid volume in women, but not men [82]. This observation of a negative correlation between selenium status and thyroid volume was confirmed in a Danish population [83], in which a trend toward increased numbers of thyroid nodules was observed with inadequate selenium status. Serum selenium status is altered in several benign and malignant diseases, including thyroiditis and Graves' disease [84]. Lower selenium levels were observed in newly diagnosed Graves' disease and autoimmune hypothyroidism [84], but correlations of selenium status with serum titers of TSH receptor (TRAK), TPO or thyroglobulin autoantibodies are less consistent [85▪▪]. The major problems with this large series of retrospective, case–control or double-blind, placebo-controlled prospective studies are the typically small number of cases, mix of women, men and various patient subgroups, short duration of intervention and follow-up monitoring, and use of several different chemical forms of selenium compounds that prevent major and broadly applicable conclusions and interpretation.

Selenium status affects major benign thyroid diseases and thyroid cancer in the following ways [7,38]:

(1) Autoimmune thyroiditis (Hashimoto's thyroiditis)
   (a) T-cell-associated thyroid destruction (Th1 induced) resulting in hypothyroidism
(2) Graves' disease (or Basedow's disease);
   (b) Hyperstimulation of the thyrocytes by TSH receptor autoantibodies (TRAK) (Th2 induced) resulting in hyperthyroidism;

(3) Iodine deficiency and goiter development/goitrogen-induced thyroid growth;
(4) Others
  (c) Postpartum thyroiditis
  (d) Silent thyroiditis
  (e) Subacute thyroiditis
  (f) Primary (idiopathic) myxoedema; and
(5) Thyroid cancer.

Thyroid diseases, both benign and malignant forms, preferentially affect women already before puberty, in their reproductive phase and also after menopause [86–89,90▪,91]. The molecular basis for this imbalance is still unclear and sex steroids may contribute but other X-chromosomal adverse (or Y-chromosomal protective) factors, X-chromosome inactivation or sex differences of the immune system *per se* might be involved. Therefore, it is of interest that thyroid-related beneficial selenium effects have been observed mainly in women in contrast to several beneficial selenium actions on other target tissues in men [38,92–95].

Limited data support the hypothesis that low selenium status [96] is associated with a worldwide increased incidence of thyroid cancer [97–99], particularly papillary thyroid cancer. In experimental animal models, epidemiological studies and some, but not all, interventional studies, marked protective effects of adequate (or even pharmacologically high) selenium concentrations against tumor initiation, progression and metastasis have been reported for several cancers, but not for thyroid cancer [39,100,101]. The proposed link between low selenium status and thyroid cancer [96,102] has recently been addressed in further epidemiological studies and a meta-analysis, but was not confirmed [103▪–105▪,106]. Again, retrospective analyses, a low number of thyroid cancer cases (<250), a single determination of selenium status and probably too short observation times may prevent clear interpretation or conclusions with impact on prevention or treatment by selenium compounds.

It also remains unclear whether decreased serum selenium levels rather are consequence and not cause of the disease state or merely associated with disease-related proinflammatory conditions, which impair expression and secretion of hepatic selenoprotein P, the major contributor to serum selenium content [40,107–109]. Alternatively, impaired selenium status and tissue supply might cause dysfunction of thyroid hormone synthesis and metabolism. Both rodent [110] and human data [83,84,111,112] indicate an interaction between iodine status and thyroid selenium content or selenoprotein expression, as partially reflected by selenium status in the blood. High iodine intake or exposure decreases thyroid selenium content and selenoprotein expression, whereas low iodine intake might be associated with elevations of thyroid selenium, selenoprotein and selenium markers in blood [5,10,15,16,38,113▪,114]

SELENIUM AND AUTOIMMUNE THYROID DISEASE

Selenium status affects T-cell differentiation. There is evidence that higher selenium favors mounting of a Th1 and regulatory T cells response [115], whereas selenium deficiency is associated with elevated Th2 cells and markers [116]. Selenium supplementation in a rat model of experimental thyroglobulin-induced autoimmune thyroiditis dose dependently attenuated Th1 response and interleukin-2 increase and reduced inflammation and thyroid tissue damage [117]. Selenium supplementation in healthy men altered leukocyte gene expression and decreased numbers of killer cell activity T cells in the blood [118]. These observations suggest beneficial effects of selenium compounds in autoimmune diseases of the thyroid [38,119,120] and other endocrine glands, and may help further understanding of the role of selenium status in inflammation, allergic reactions and asthma. In women at risk for postpartum thyroiditis, adequate selenium status prevents its development. In a prospective placebo-controlled double-blind preventional study [121], not yet confirmed [113▪], there were fewer cases of postpartum thyroiditis and hypothyroidism.

From several interventional studies in various countries that have examined several selenocompounds, doses and time of administration, there has been no evidence to support any direct effect of increased selenium intake on thyroid hormone and TSH serum concentrations [7,25,94,122], although most of these studies were not done in individuals with severe selenium deficiency. This indicates that deiodinase selenoproteins in peripheral tissues and anterior pituitary thyrotropes are adequately supplied with selenium even under conditions of marginal selenium deficiency. In contrast, stimulating effects of selenium on deiodinase expression are clearly demonstrated in severe selenium deficiency using animal experimental and cell culture models.

Several prospective, placebo-controlled and double-blind studies have been performed to improve quality of life, well-being, thyroid hormone status and disease symptoms of autoimmune thyroiditis or pregnancy [113▪,123]. Recent meta-analyses have summarized the diverse findings of four of these studies performed in areas of different

iodine intake, unclear basal selenium status and in different patients groups, such as newly diagnosed disease, patients already treated with thyroid hormone and individuals with very different antibody titers [85▪▪,119]. Although initial studies clearly demonstrated decreased thyroid antibody titers and increased quality of life after at least 3 months of treatment with high doses of selenite or selenomethionine, subsequent reports were more ambiguous. In general, most of these studies were underpowered, too short or with too broad inclusion criteria to draw clear conclusions. For Graves' disease, only one major multicentric prospective, placebo and serum-controlled study demonstrated improved quality of life and disease activity scores [124]. At present, several confirming studies are ongoing for both autoimmune thyroiditis and Graves' disease [125,126] (see also https://clinicaltrials.gov/ct2/show/NCT02112643?term=selenium+and+thyroid).

SELENIUM STATUS AND RELEVANT BIOMARKERS

Adequate selenium intake, with respect to proper thyroid function or other beneficial health effects, can be monitored by analysis of serum or plasma selenoproteins [e.g. selenoprotein P or plasma glutathione peroxidase 3 (pGPx3)] [127–131]. pGPx3 is secreted by the kidney, whereas circulatory selenoprotein P is mainly of hepatic origin. Careful analysis of selenium status and levels of selenoproteins in serum or plasma revealed that plateau levels of pGPx3 (pGPx3 >125 μU/l) are reached at 1 μM selenium concentration in the blood (125 μg selenium intake/day). Higher selenium intake is needed for maximal levels of selenoprotein P, which are reached beyond >125 μg/l of selenium. Maximal levels of both GPx3 and selenoprotein P may provide best systemic protection and function of selenium-dependent processes. Selenoprotein P is the major selenoprotein in plasma, accounting for up to 70% of plasma selenium, and is crucial for the specific distribution and transport of selenium to several target tissues, which need adequate selenoprotein P concentrations to supply selenium to tissues dependent on receptor-mediated selenoprotein P delivery [34,130–134,135▪▪]. Impaired selenoprotein P status has been observed in several pathologic conditions, including negative acute-phase reactions, inflammation and various cancers, and experimental animal models [40,107–109]. Determination of GPx1 activity in erythrocytes might provide a long-term indicator of selenium based on the lifetime of erythrocytes. Determination of selenium by fluorescence methods, inductively coupled plasma mass spectrometry or atom absorption spectrometry in serum, plasma, whole blood or body fluids provides an integral measure of selenium supply, but lacks specific information of biomarkers, such as hepatic selenoprotein P or renal pGPx3. Analysis of selenium status from hair or nails is not recommended because of artifacts resulting from cosmetic or external application of selenium-containing compounds.

Thyroid selenium content and selenoprotein expression are typically not reflected by serum selenium status [5–7,21,31,36,38]. This suggests that analyses of serum, plasma or erythrocyte selenium content do not necessarily reflect tissue or cell-specific selenium content or selenoprotein expression, which may be altered by transmembrane transport of selenium compounds or by ApoE2 receptor-mediated targeting of selenium-rich selenoprotein P [33▪▪]. Tissue and cell-dependent expression profiles of selenoproteins might differ from each other and from selenium biomarker levels in blood. These profiles might be concordant or discordant with selenium status represented by serum selenium levels. These observations suggest the need to develop and validate tissue-specific biomarkers and endpoints of selenium bioavailability and cellular action. There is no selenium-related parameter that has been established for the thyroid gland or systemic and cellular thyroid hormone action. Selenoprotein gene polymorphisms in many human populations living on different nutritional selenium intake provided evidence of genetic adaptation to inadequate nutritional supply [136▪].

Plasma selenium markers are different in individuals of low-income classes on inadequate nutrition as recently demonstrated between black and white Americans or among individuals with different genetic variants in selenoprotein P gene [137–139]. Furthermore, apart from nutritional intake of selenium, iodine and the other trace elements essential for thyroid hormone synthesis and thyroid function and also involuntarily exposure to nutritional and environmental endocrine active compounds ('endocrine disrupters') might interfere with and disturb thyroid hormone homeostasis [140–142]. Ongoing functional and genetic analysis of genes and their encoded protein variant, for which no biological or enzyme function has yet been identified [143▪], will add to a better understanding of the distinguished role of the essential trace element selenium to thyroid hormone synthesis and action, hormonal homeostasis as well as prevention and treatment of thyroid-related diseases.

CONCLUSION

Selenium compounds and selenoproteins protect the thyroid gland from H_2O_2 and ROS damage.

Thyroid hormone synthesis and metabolism represent a remarkable example of coevolution of biology and function of three essential trace elements: iodine, selenium and iron. Many studies, primarily of women, have shown that adequate selenium status benefits thyroid-related diseases. Low selenium status is observed in patients with newly diagnosed Graves' disease and autoimmune thyroiditis. The possible mechanisms of action of selenoproteins in benign and malignant thyroid disease, and the action of selenocompounds in thyrocytes, endothelial cells, angiofollicular units and/or immune cells remain to be established. Nutritional, environmental, genetic, life-phase and disease-related factors modulate the fine-tuned interaction between the three trace elements, selenium, iodine and iron, thyroid function and thyroid hormone homeostasis and thus play an important role in maintenance of human health, prevention and treatment of diseases.

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Conflicts of interest

There are no conflicts of interest.

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